Exhibit 7

Editorial

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Understanding and Preventing (*N*-Nitrosodimethylamine) NDMA Contamination of Medications

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Abstract

N-nitrosodimethylamine (NDMA) is a hepatotoxic agent and carcinogen contaminant in commonly used medications such as valsartan, losartan, irbesartan, and ranitidine. NDMA can be produced during manufacture, introduced from contaminated ingredients procured elsewhere, or introduced from contaminated solvents and catalysts. The Food and Drug Administration has established a maximum dose of NDMA that is permissible per tablet and guidance for manufacturers. However, many unanswered questions about NDMA contamination need rigorous investigation.

Keywords

NDMA, contamination, FDA, drug safety, manufacturing

Introduction

As of the last Food and Drug Administration (FDA) update on September 23, 2019, a total of 1159 lots of valsartan, losartan, and irbesartan had been recalled because they contained unacceptably high levels of *N*-nitrosodimethylamine (NDMA) or other nitrosamines such as *N*-nitrosodiethylamine (NDEA).[1] On October 15, 2019, the FDA posting a warning letter for Torrent Pharmaceuticals, a manufacturer of losartan, about several manufacturing violations at one of their plants. The warning letter includes failure to follow written procedures for production/process control and failure to adequately investigate batch discrepancies.[2]

NDMA contamination has now extended outside the angiotensin receptor blocker (ARB) drug class. On September 13, 2019, the FDA first warned consumers that some ranitidine products also contain unacceptably high NDMA levels and were are being recalled.[3] Many manufacturers, including Apotex Corporation, Sandoz, Sanofi, Aurobindo, and Dr Reddy Labs, have had to recall products containing ranitidine because of the high levels of NDMA.[3,4]

What Are the Pharmacological Mechanisms for NDMA Harm?

NDMA has been shown to cause liver damage and fibrosis in animal models.[5,6] In one animal model, exposure to NDMA caused centrilobular congestion, Kupffer cell hyperplasia, and liver fat accumulation after 7 days and severe neutrophilic infiltration, multifocal collapse of liver parenchyma, and deposition of collagenous fibrosis after 14 days.[6] There are cases where people around the world have been intentionally poisoned by unknowingly ingesting several hundred milligrams of NDMA, resulting in diarrhea, vomiting, hepatotoxicity, and/or death.[7,8]

The International Agency for Research on Cancer has classified NDMA as a probable carcinogen, with animal studies finding tumor formation predominantly in the gastrointestinal tract and liver but also in the lungs and kidneys.[8,9] NDMA, like other nitrosamine contaminants, activates ras oncogenes, and NDMA metabolism by CYP2E1 creates methyldiazonium, a known mutation inducer via methylation.[8-10] As such, NDMA is suspected to cause both localized and systemic carcinogenic effects.[9,10]

Where Does NDMA Come From?

NDMA was previously used in production of liquid rocket fuel, lubricants, and sealants but is now only created as a byproduct of chemical reactions, such as those that involve reactions between alkylamines/dimethylamine and nitrogen oxides, nitrous acid, nitrite salts, chloramines, bromamines, or hypochlorite.[11,12] NDMA is produced in many water supplies from the interaction of the water disinfectant chloramine with

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nitrogenous compounds that are in the water itself or water processing equipment such as rubber seals.[13]

NDMA is also present in alcoholic beverages, cereals, dairy, fish, meat, fruits, and vegetables.[14,15] This NDMA contamination could arise from the water the plants and animals utilize, soil contamination of the food or the food the animals ate, or during processing before sale. Food can contain little to no NDMA all the way up to ~1700 ng/kg by product weight. All told, it is estimated that the average infant, child, and adult consume 70, 100, and 110 ng/d of NDMA from water and food sources, respectively.[14,15]

There are 2 main sources of NDMA contamination in medications.[16-18] The first source is the use of material contaminated with NDMA in the manufacturing process.[16] Solvents or catalysts may pose a risk for nitrosamine formation when the amines in the chemicals are sent for recovery and treated with nitrous acid before coming back to the manufacturer for reuse. If independent recovery facilities comingle solvents or catalysts collected from different manufacturers before recovery, including one that is producing high concentrations of NDMA, the redistributed chemicals would be contaminated as well. If the solvents or catalysts from different manufacturers are recovered sequentially without adequate cleaning of equipment between customers, the contaminated residual NDMA is incorporated into the newly treated solvents or catalysts. This explains why some ARB producers have identified NDMA in their finished active pharmaceutical ingredient (API), even though they are using processes incapable of forming them.[16] The second source of contamination occurs when NDMA can be created from an intermediate or from the active ingredient itself.[16,17] Ranitidine contains both a nitrite group and a dimethylamine group and the nitrosation of ranitidine was found to create NDMA under stomach-relevant pH conditions in vitro.[17,18]

How Much NDMA Is Safe to Consume?

The amount of NDMA in the water supply is usually very low, with acceptable amounts set at 100 ng/L according to the World Health Organization (WHO) but only 40 ng/L in Canada.[13] It is estimated that at a daily ingestion of 1.9 L of water with an NDMA concentration of 13 ng/L (26 ng/d) that the resulting cancer risk after 70 years has an upper bound of 1 in a million people. At 40 ng/L of NDMA (76 ng/d), the resultant cancer risk over this time period has an upper bound of 1 in 100 000.[13]

The FDA has set an interim acceptable level of NDMA in a medication tablet or capsule at 96 ng/d.[2] Although this is below the 190 ng dose of NDMA that the WHO would find acceptable (1.9 L of 100 ng/L of water), it is estimated that senior citizens (≥65 years old) take a median number of 4 medications daily, so there is a multiplicative risk of NDMA exposure over time in these patients (384 ng/d exposure if each tablet contained 96 ng of NDMA).[13,19] This NDMA exposure is in addition to that contained in the patients' water and food.

How Much NDMA Was Found in ARBs and Ranitidine?

The NDMA daily dosages in 17 valsartan products were assessed by the FDA[20]: 9 products had levels below the level of detection, 3 products had NDMA doses ranging from 330 to 620 ng/tablet, and 5 products had lots with NDMA doses ranging from 6940 to 20 190 ng/tablet. Even from products by the same manufacturer, different exposures were seen with different products. For example, valsartan 160- and 320-mg products from Torrent Pharmaceuticals contained 450 to 620 ng/tablet, but the valsartan 320 mg + amlodipine 10 mg + hydrochlorothiazide 25 mg combination product had 10 240 to 11 530 ng/tablet.[20]

Valisure, an online pharmacy, found NDMA doses in some ranitidine products of 23 600 to 304 500 ng/tablet and alerted the FDA.[21] The FDA states that the high temperature (266°F) gas chromatography/mass spectrophotometry method used in Valisure's laboratory is not suitable because heating the sample generates NDMA.[4,18,21] The FDA's preferred method, liquid chromatography–high-resolution mass spectrometry, does not use heating, and although it found markedly lower NDMA doses per tablet for ranitidine, it still found doses that were unacceptably high.[22] In a recent analysis reported by FDA, levels of NDMA from products arising from various manufacturers ranged from 0 ng/tablet to a maximum of 860 ng/tablet.[23] In all, 9 products had at least some lots with NDMA doses exceeding 96 ng/tablet, 5 had NDMA doses exceeding 300 ng/tablet, and 3 had NDMA doses exceeding 500 ng/tablet.[23]

What is not known, but potentially concerning, is whether the ranitidine in these tablets is readily converted into NDMA when the tablets are heated during storage, transport in a car on a summer day, or by the sun after home mail order delivery.[4,18] In 2016, urine samples were collected from 5 female and 5 male adults over 24 hours before and after consumption of ranitidine 150 mg tablets. Following ranitidine intake, the urinary NDMA increased from a baseline of 110 to 47 600 ng/d.[4,19] It is not clear to what extent the NDMA was created by degradation of the tablets outside the body or produced by the body after ingestion. The FDA reported a summary of tests simulating the gastric and intestinal environment and were unable to produce NDMA with the introduction of ranitidine.[22] However, the specifics of what was done in these simulations is not disclosed, and they admit that only human studies can truly answer this question.[22]

What Should Be Done to Protect Patients?

The FDA provided rigorous and prudent general advice to manufacturers of ARBs.[17] In essence, manufacturers of either API or finished ARB drug products should test a representative sample of each lot produced. Testing should include batches already distributed that have not yet reached their labeled expiration date as well as those not yet distributed. Any batch already in distribution, with an NDMA level that exceeds the FDA published interim acceptable limit, should be recalled. Although not the focus of this editorial, the same would be true of NDEA as well. Manufacturers of finished drug products using API from another manufacturer should test each API lot received before creating tablets or capsules.[17]

In addition to this FDA guidance, more could also be done. The FDA needs to move beyond reactively waiting until they are alerted to NDMA issues from outside groups and proactively alert manufacturers of ingredients, such as ranitidine, that have chemical structures prone to the creation of NDMA. The FDA is starting to take these actions.[22] For example, FDA has disclosed that nizatidine has a chemical structure similar to ranitidine's and might also be prone to NDMA production during manufacture. The FDA is calling on manufacturers of nizatidine to test their own products and send samples to them for testing as well.[22]

API and any inactive ingredients prone to NDMA formation should be tested under different environmental conditions to determine how product storage, especially heating, light exposure, and time since manufacture, can affect NDMA creation. If issues are found, limits on the expiration date and/or cautionary language about proper storage of the drugs should be identified. For these higher-risk APIs, the FDA should determine how much NDMA is created by the body after ingestion in general terms and if any factors such as age, ethnicity, stomach pH, or microbiota differences affect the amount created.

I applaud pharmacy groups who are inspecting some of their drugs for NDMA contamination because it is not being adequately assessed by manufacturers.[18] Such testing should continue or even intensify. Clinicians should avoid ranitidine because we cannot determine the extent of NDMA creation that may result after manufacture and because there are myriad other choices for reflux and gastromucosal protection.[22] The FDA has found that famotidine, cimetidine, omeprazole, lansoprazole, and esomeprazole products have not shown NDMA contamination to date.[22] It is also prudent to use these alternatives preferentially over nizatidine until testing is completed.

In a recent FDA statement, they write that the amount of NDMA found in ranitidine is in line with eating a large steak.[22] Although I know they are trying to avoid panic, they should not be so dismissive of the nature of this issue either. A 1-kg steak has ~700 ng of NDMA, but few people eat that much steak and not on a chronic basis.[15] The chronic use of ranitidine, with NDMA dosages of 560 to 860 ng/tablet, on top of other NDMA-contaminated medications and added to the basal NDMA exposure from food and water, does not seem to pose inconsequential risk, and if it did, the FDA would not be supporting product recalls.[14,15,22,23] This is not to mention the unknown potential for NDMA exposure in dietary supplements and the probable exposure in some cosmetics and personal care products.[8] The FDA should also work with other federal agencies to more clearly quantify the risk that chronic heightened exposure to NDMA in our drug supply could pose.

Conclusions

The NDMA dosage in drugs from the ARB class and with ranitidine ranged from the acceptable <96 to 20 190ng/tablet. These very high NDMA exposures could occur over a long period of time for the treatment of hypertension or chronic gastroesophageal reflux and could be compounded if multiple drugs with this contamination are being taken. The extent of our drug supply that is tainted with NDMA is not fully known, and because it can be introduced by reuse of solvents and catalysts intermingled with that from other manufacturing plants, it cannot be entirely predicted by the known chemical reactions required to create the API. The FDA has acted appropriately hence far, but there may be more that can be done to improve our knowledge in this area and to limit human exposure to NDMA through our prescription drugs.

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